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This is a pre print version of the following article:

Original Citation:

Availability:

This version is available <http://hdl.handle.net/2318/1779745> since 2021-03-12T13:11:38Z

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Increased serum ferritin levels predict long-term mortality in patients with NAFLD

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Background and Aim: Hyperferritinemia is a common feature in patients with non-alcoholic fatty liver disease (NAFLD) and correlates with the severity of liver fibrosis. Our aim was to assess the impact of ferritin on long-term outcomes and survival in a large cohort of NAFLD patients.

Methods: We included 1247 patients with biopsy-proved NAFLD in tertiary centers in Italy (Turin, Milan, Rome, Palermo), Australia (Sydney) and UK (Newcastle). Clinical and biochemical data were collected at the time of liver biopsy. Ferritin levels ≤ 300 $\mu\text{g/L}$ for men and ≤ 200 $\mu\text{g/L}$ for women were considered as upper limit of normal (ULN). Clinical outcomes, including liver-related events (ascites, encephalopathy, variceal bleeding) and survival, were collected after a median follow-up of 90 months.

Results: The median age of the study cohort was 48 [IQR 38-57] years and 814 (65.3%) patients were males. The prevalence of obesity and type 2 diabetes was 45.0% and 28.1%. Overall, hyperferritinemia was found in 373 (29.9%) patients; severe fibrosis ($F \geq 3$) was found at liver biopsy in 272 (21.8%) patients while NASH was diagnosed in 756 (60.6%) of cases. Serum ferritin $> 2 \times \text{ULN}$ resulted significantly associated with $F \geq 3$ (OR = 2.10, 95%CI 1.40-3.14, $p < 0.001$). After a median follow-up of 90 months, 24 patients (2.3%) died and 57 (4.8%) developed liver-related events. At univariate analysis, the incidence of liver-related events and mortality varied significantly according to serum ferritin values $> 2 \times \text{ULN}$ (Log-rank test: $p = 0.004$ and $p = 0.001$, respectively). However, at multivariate Cox regression analysis adjusted for age, body mass index, diabetes and fibrosis, ferritin levels $> 2 \times \text{ULN}$ independently predicted mortality (HR = 3.04, 95%CI 1.16-7.93, $p = 0.023$) but not liver-related events (HR = 1.67, 95%CI 0.90-3.11, $p = 0.105$).

Conclusions: Ferritin levels higher than $2 \times \text{ULN}$ are associated to severe liver fibrosis in NAFLD patients and are able to predict longterm mortality.

This work has received support from the EU/EFPIA Innovative Medicines Initiative 2 Joint Undertaking (LITMUS grant no. 777377).